6. (amended) The method of claim 1 wherein the molecule to be delivered is a nucleic acid molecule and the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense and the nucleic acid molecule is delivered directly to the endothelium of large vessels.

16. (twice amended) The conjugate of claim 13 wherein the molecule to be delivered is a nucleic acid molecule in combination with means for delivering the nucleic acid molecule directly to the endothelium of large vessels.

17. (amended) The conjugate of claim 16 wherein the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell in combination with means for delivering the nucleic acid molecule directly to the endothelium of large vessels.

18. (amended) The conjugate of claim 16 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense in combination with means for delivering the nucleic acid molecule directly to the endothelium of large vessels.

Remarks

Allowance of Claims and Withdrawal of Rejections

Allowance of claims 13-15 and 20-25 is greatly appreciated, as are the withdrawal of rejections of claims 1-25 under 35 U.S.C. §112 and under §102 or 103 other than as noted below.

Rejections under 35 U.S.C. §112, first paragraph

Claims 5-7 and 16-19 were rejected under 35 U.S.C. §112, as non-enabled by the specification for *in vivo* delivery of genes to cells. This rejection is traversed if applied to the amended claims

The basis of the argument is that even though the application demonstrates that conjugates of molecules binding to the endothelial protein C receptor (EPCR) can be made, delivered to cells, the conjugates bind to the EPCR, and the molecules be taken up by the EPCR and delivered into the nucleus, that one skilled in the art could not perform this method *in vivo*, since all of the examples use *in vitro* delivery of the genes.

Although not agreeing with the Examiner's conclusions, claims 5 and 6 have been amended to recite that "the nucleic acid molecule is delivered directly to the endothelium of large vessels". This should moot any issue relating to the unpredictability of the delivery of the genes via systemically.

Claims 16, 17 and 18 have been similarly amended to recite that the nucleic acid is in combination with means for delivering the nucleic acid molecule directly to the endothelium of large vessels. These are known and can include a syringe or catheter for direct administration to the blood vessel endothelium during an outpatient procedure or during surgery.

Claim 7 is believed to have been rejected in error since this claim is drawn to drugs or diagnostic agents, and there is no unpredictability of the administration of drugs or diagnostic agents systemically or by any other appropriate method. This is also true of claim 19.

Rejections under 35 U.S.C. §102(b)

Claims 1, 3, 8, and 10-12 were rejected under 35 U.S.C. §102(b) as disclosed by WO 96/05303. This rejection is respectfully traversed if applied to the amended claims.

The claims have been amended to recite that the molecule to be delivered is active in the nucleus of the endothelial cell. This excludes the prior art which discloses an agent such as activated protein C, since activated protein C is active in the blood not in the nucleus.

Rejections under 35 U.S.C. §102(e)

Claims 1, 3, 8 and 10-12 were rejected under 35 U.S.C. §102(e) in view of U.S. patent Nos. 5,695,993 and 5,852,171 to Fukudome, et al. This rejection is respectfully traversed if applied to the amended claims.

None of the patents disclose a conjugate of a molecule which is active in the nucleus. Therefore the prior art does not disclose the claimed method or conjugate.

Rejections under 35 U.S.C. §103

Claims 1-4 and 8-12 were rejected under 35 U.S.C. §103 as obvious over WO 96/05303, U.S. Patent No. 5,695,993 or U.S. Patent No. 5,852,171 to Fukudome, et al. in combination with Jans, et al., BioEssays 20, 400-411 (1998) and Rosenkranz, et al.These rejections are respectfully traversed is applied to the amended claims.

As discussed before, none of the primary references disclose a conjugate of a compound selectively binding to EPCR with a molecule to be delivered to the nucleus *where the molecule is active in the nucleus*. None of the prior art recognizes that the conjugate results in transport into the nucleus therefore it cannot be obvious to make a conjugate of a molecule which will be active in the nucleus.

Although Jans, et al., disclose that certain molecules, such as some growth factors and cytokines, bind to cell surface receptors where they are internalized into the nucleus, to participate in gene regulation. This says nothing about conjugates which are not naturally occuring molecules such as growth factors and cytokines, large vessel endothelium, EPCR and molecules specifically binding thereto, which are not cytokines nor growth factors. Accordingly, there is no teaching that would lead one to substitute EPCR for the receptors of Jans and Hassan, nor molecules which bind to EPCR for the cytokines and growth factors of Jans and Hassan to transport molecules which are active in the nucleus, into the nucleus.

In summary, none of the cited art discloses the claimed conjugates or methods of use thereof. Moreover, none makes obvious the claimed conjugates or methods of use since there is no teaching that would lead one skilled in the art to believe that EPCR would mediate uptake and transport to the nucleus of molecules which are active in the nucleus.

Allowance of claims 1-25, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix to facilitate review by the examiner.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Dated: March 21, 2000

ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 W. Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8794
(404) 873-8795 (fax)

Certificate of Mailing under 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: March 21, 2000

Jean Hicks